Preclinical Characterization of a Novel PI3Kα H1047R Mutant Selective Inhibitor

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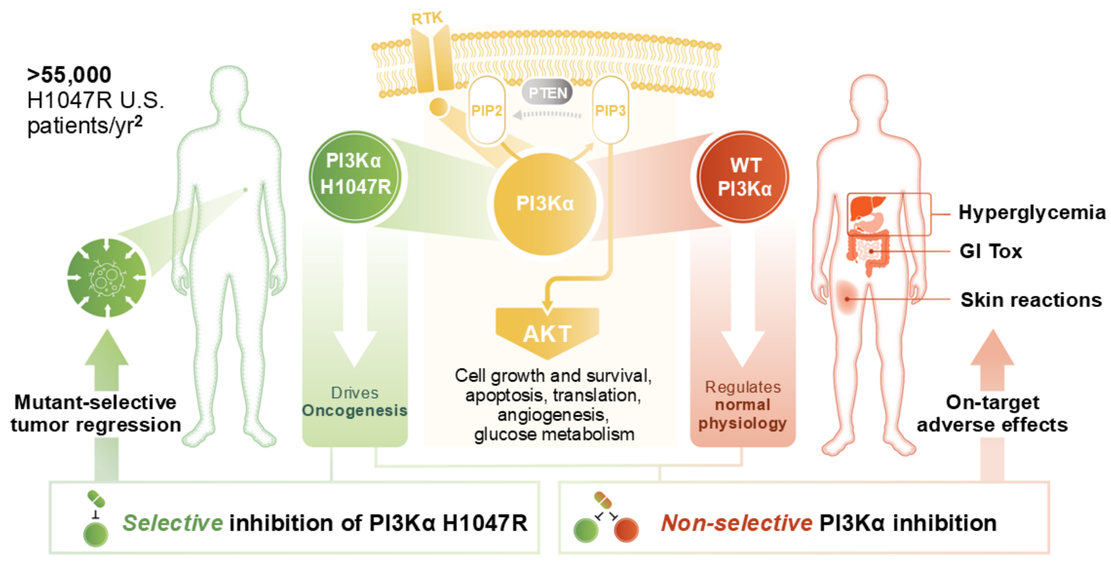
Selective PI3Kα H1047R Inhibition Avoids PI3Kα Wild Type Toxicity for Improved Efficacy and Tolerability

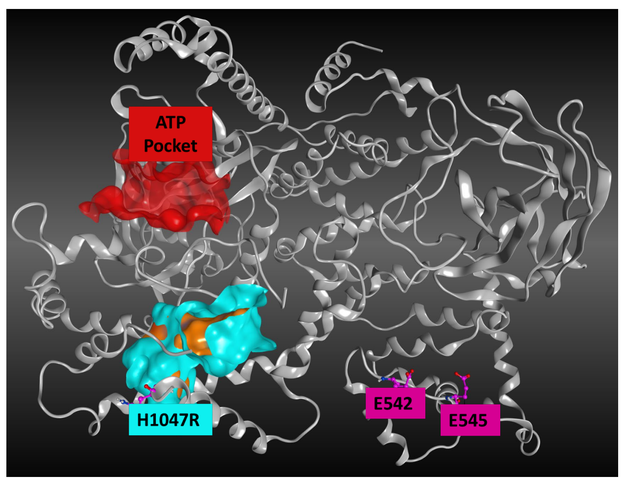


- On-target inhibition of wild type PI3Kα by approved inhibitors leads to tolerability issues including hyperglycemia, hyperinsulinemia, gastrointestinal issues, and skin reactions[1]
- Increases in insulin result in activation of PI3Kα in tumor cells and diminished efficacy[1]
- A mutant selective inhibitor that avoids these toxicities may result in better tolerability, greater target coverage, and improved efficacy compared to approved agents

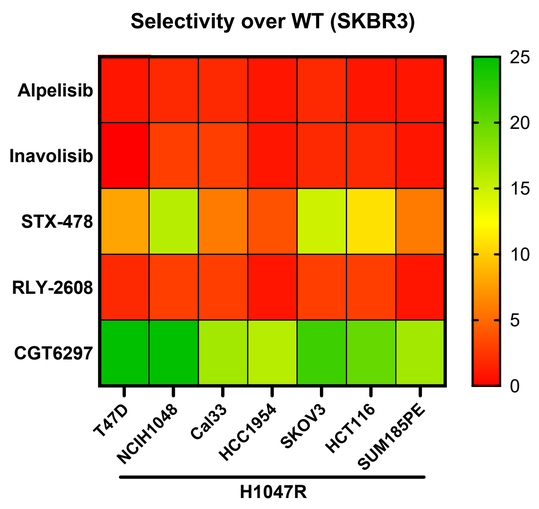
CGT6297 Key Findings and Conclusions

- Potent allosteric kinase domain inhibitor of mutant PI3Kα H1047R with 25-fold selectivity over PI3Kα WT. This preclinical lead has high oral bioavailability and low clearance across species providing robust inhibition of downstream signaling and efficacy in animal models dosed orally.
- X-Ray crystal structure of CGT6297 bound to PI3Kα H1047R protein shows binding in the H1047R allosteric pocket with no binding in the ATP pocket
- In a panel of mechanistic cellular assays measuring inhibition of pAKT, CGT6297 had nM inhibition on H1047R mutant lines with 25x selectivity over the SKBR3 PI3Kα WT line
- Linear dose ascending PK was observed with high oral bioavailability and low clearance across preclinical species
- 90% Inhibition of pAKT in the PI3Kα H1047R NCI H1048 (lung carcinoma) PD mouse model with no significant increase in insulin compared to alpelisib at its clinically relevant dose of 20 mg/kg[3]
- Superior efficacy compared to a 50 mg/kg dose of alpelisib (exposure at this dose is above the clinically achievable exposure) in the PI3Kα T47D HR+ HER2- breast mouse tumor growth inhibition model
- Further assessment of the Cogent PI3Kα selective lead series continues

PI3Kα H1047R Allosteric Kinase Domain Mutant Selective Inhibitor

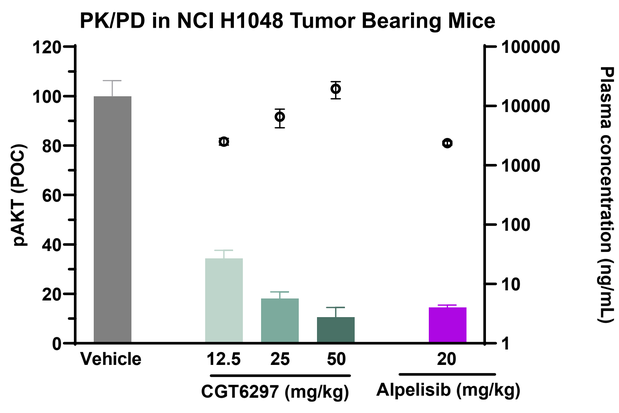


- 2.4Å Resolution crystal structure of CGT6297 bound to mutant PI3Kα H1047R protein
- CGT6297(orange) binds in the H1047R kinase domain allosteric site shown as a cyan surface
- ATP pocket is shown in the red surface
- The helical mutation residues E542 and E545 are shown for illustrative purposes

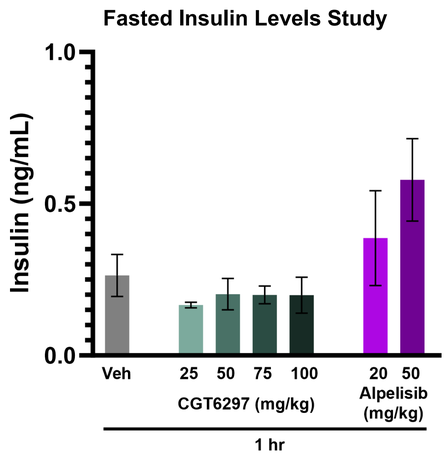


- CGT6297 was tested in a panel of PI3Kα H1047R mutant and PI3Kα WT mechanistic cell assays measuring inhibition of pAKT
- Low nM potency was observed for CGT6297 across PI3Kα H1047R mutant lines
- CGT6297 is selective for PI3Kα H1047R over PI3Kα WT with a selectivity window of 25x comparing mutant to WT SKBR3
- Alpelisib, Inavolisib, and RLY-2608[4] have no selectivity over WT; STX-478[5] shows 10x mutant to WT selectivity in this assay

Dose-Responsive Inhibition of pAKT With No Increase in Insulin

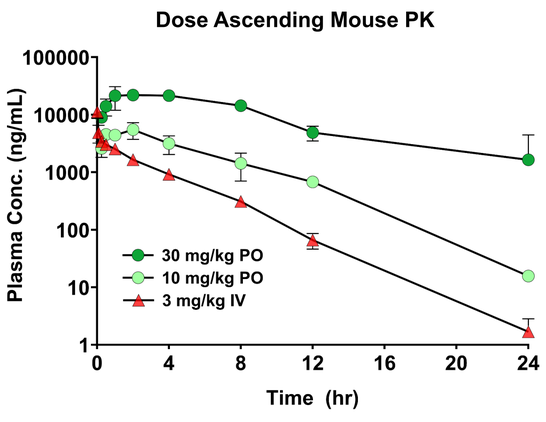


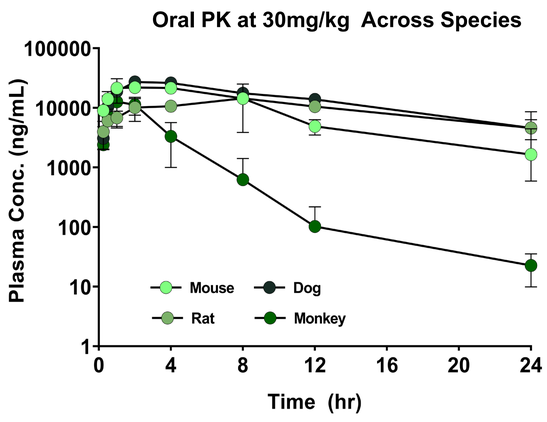
- In a PK/PD experiment measuring inhibition of pAKT, CGT6297 was dosed orally at 12.5, 25, and 50 mg/kg to PI3Kα H1047R mutant NCI H1048 (lung carcinoma) tumor bearing mice
- CGT6297 showed dose responsive inhibition of pAKT with 90% pAKT inhibition at 4 h at the 50 mg/kg dose
- The $EC_{50,free}$ for CGT6297 was calculated to be 15 nM
- Alpelisib was dosed at the clinically matched exposure (20 mg/kg)[3] and showed 85% pAKT inhibition



- Insulin levels were measured 1 hour post dose in a fasted mouse study to compare PI3Kα wild type sparing CGT6297 to nonselective alpelisib
- No elevation of insulin was observed at the 25-100 mg/kg doses of CGT6297
- Alpelisib showed an increase of insulin compared to vehicle control at both 20 and 50 mg/kg in this study

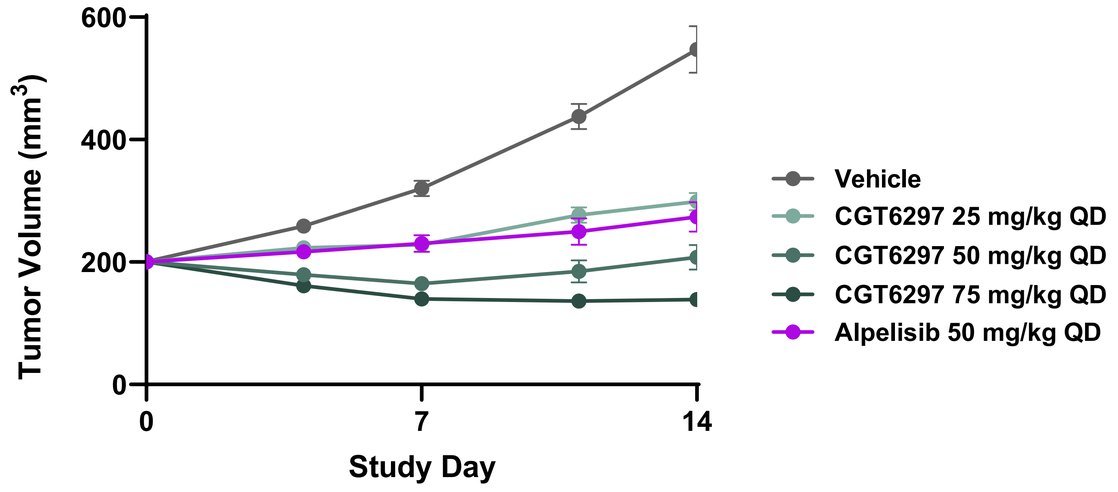
Dose Ascending Pharmacokinetics With High Oral Bioavailability and Low Clearance





- CGT6297 demonstrates linear oral dose ascending mouse PK
- Clearance of 5% ER dosed at 3 mg/kg IV
- Oral bioavailability (%F) ranged from 95% to >100%
- Similar dose ascending PK was observed across preclinical species
- CGT6297 shows high oral bioavailability and low clearance in mouse, rat, dog, and cyno
- Oral bioavailability (%F) ranged from 60% to >100% dosed at 30 mg/kg
- Clearance ranged from 3% to 19% ER dosed at either 1 or 3 mg/kg IV

Regressions in a T47D PI3Kα H1047R Breast Cancer Model



- In a TGI experiment measuring tumor volume, CGT6297 was dosed PO QD at 25, 50 and 75 mg/kg to PI3Kα H1047R mutant T47D (HR+ HER2- Breast) tumor bearing mice for 14 days
- The 25 mg/kg dose of CGT6297 showed similar efficacy to the 50 mg/kg dose of alpelisib
- The 50 mg/kg and 75 mg/kg doses of CGT6297 have superior efficacy compared to 50 mg/kg QD dose of alpelisib[3]
- Exposure at the 50 mg/kg dose of alpelisib is above the clinically achievable exposure

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